Electronic Supplementary Information

Thermo- and Oxidation-Responsive Supramolecular Vesicles Constructed from Self-assembled Pillar[6]arene-Ferrocene Based Amphiphilic Supramolecular Diblock Copolymers

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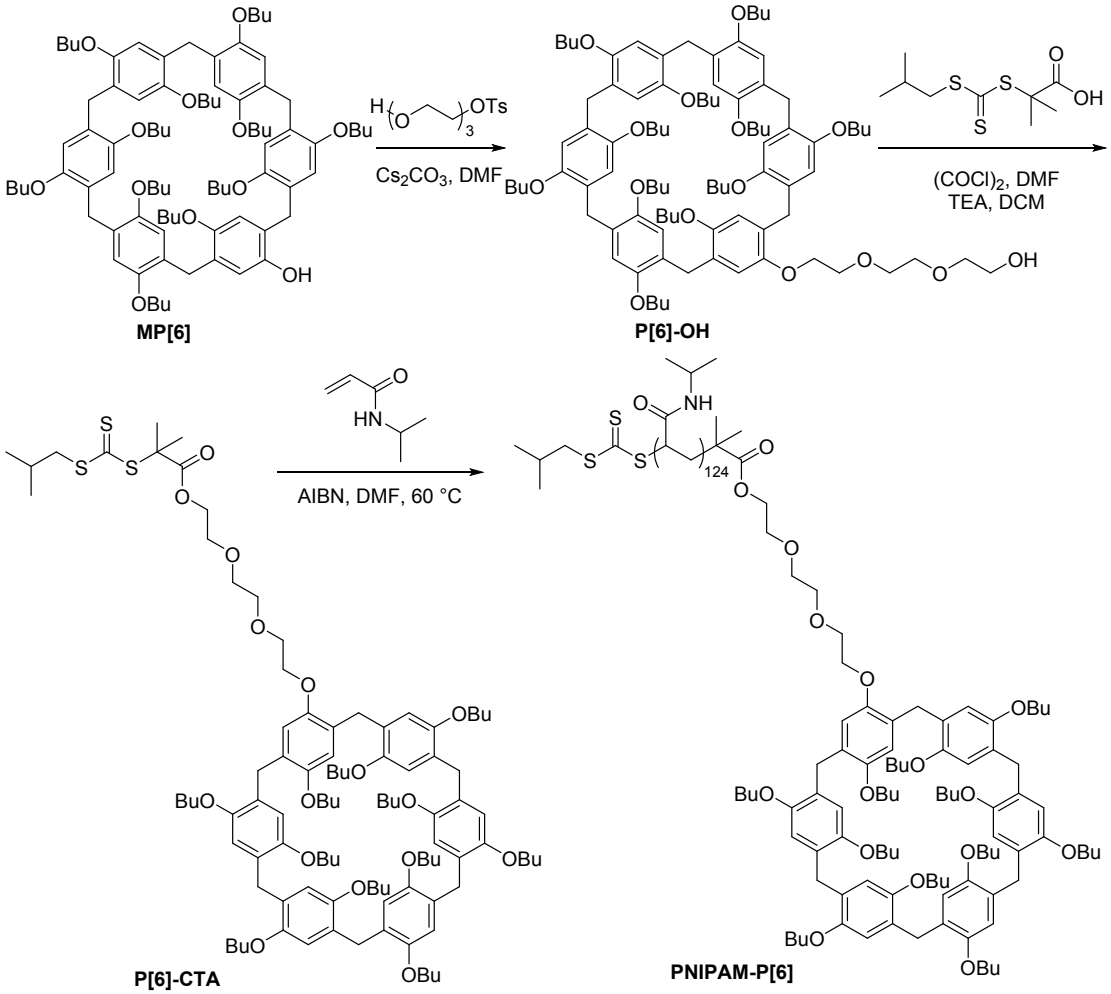
Table of Contents

1. Synthetic procedures

1.1 Synthesis of poly(*N*-isopropylacrylamide)-pillar[6]arene (PNIPAM-P[6])



Scheme S1. Synthetic routes of pillar[6]arene end-functionalized polymer **PNIPAM-P[6]**

1.1.1 Synthesis of mono-triethylene glycol dibutyl-pillar[6]arene (P[6]-OH)

To a solution of mono-deprotected per-butyl-pillar[6]arene (0.80 g, 0.60 mmol) and triethylene glycol mono-tosylate (0.54 g, 1.78 mmol) in dry DMF (15 mL), Cs_2CO_3 (1.54 g, 4.7 mmol) was added under argon. The mixture was stirred at 65 ºC for 24 h. After the reaction was finished, the solvent was removed at 55 ºC under vacuum. The residual was dissolved in dichloromethane (200 mL), washed with water (3 × 200 mL), brine, and dried over anhydrous Na_2SO_4. The crude product was purified by silica-gel column chromatography (PE/EA = 10:1, v/v) to afford the pure product **P[6]-OH** as a yellow oil (0.67 g, 0.41 mmol，68.3%). ^{1}H NMR (400 MHz, $CDCl_3$,

298 K) δ(ppm): 6.77 – 6.58 (m, 12H, Ar*H*), 3.97 (t, *J* = 4.8 Hz, 2H, –OC*H*$_2$–), 3.84 – 3.61 (m, 42H, Ar–C*H*$_2$–Ar & Ar–OC*H*$_2$– & –OC*H*$_2$C*H*$_2$O–), 3.58 (t, 2H, –C*H*$_2$OH), 1.76 – 1.56 (m, 22H, Ar–OCH$_2$C*H*$_2$–), 1.51 – 1.32 (m, 22H, –C*H*$_2$CH$_3$), 0.95 – 0.81 (m, 33H, –C*H*$_3$). ^{13}C NMR (100 MHz, $CDCl_3$, 298 K) δ(ppm): 151.1, 150.5, 150.5, 150.5, 150.5, 149.9, 128.4, 128.1, 127.9, 127.9, 127.9, 127.8, 127.8, 115.9, 115.2, 115.1, 115.1, 115.0, 115.0, 114.9, 114.8, 114.6, 72.6, 70.9, 70.5, 70.2, 68.6, 68.4, 68.2, 68.2, 68.2, 68.0, 61.8, 45.2, 32.0, 32.0, 31.9, 31.9, 31.9, 31.0, 30.9, 30.8, 30.8, 30.6, 27.9, 25.3, 22.1, 19.5, 19.5, 19.4, 19.4, 14.0, 14.0, 13.9. HR-ESI-MS: *m/z* Calcd for $C_{95}H_{138}O_{16}Na$ $[M+Na]^+$: 1503.9771; found: 1503.9775.

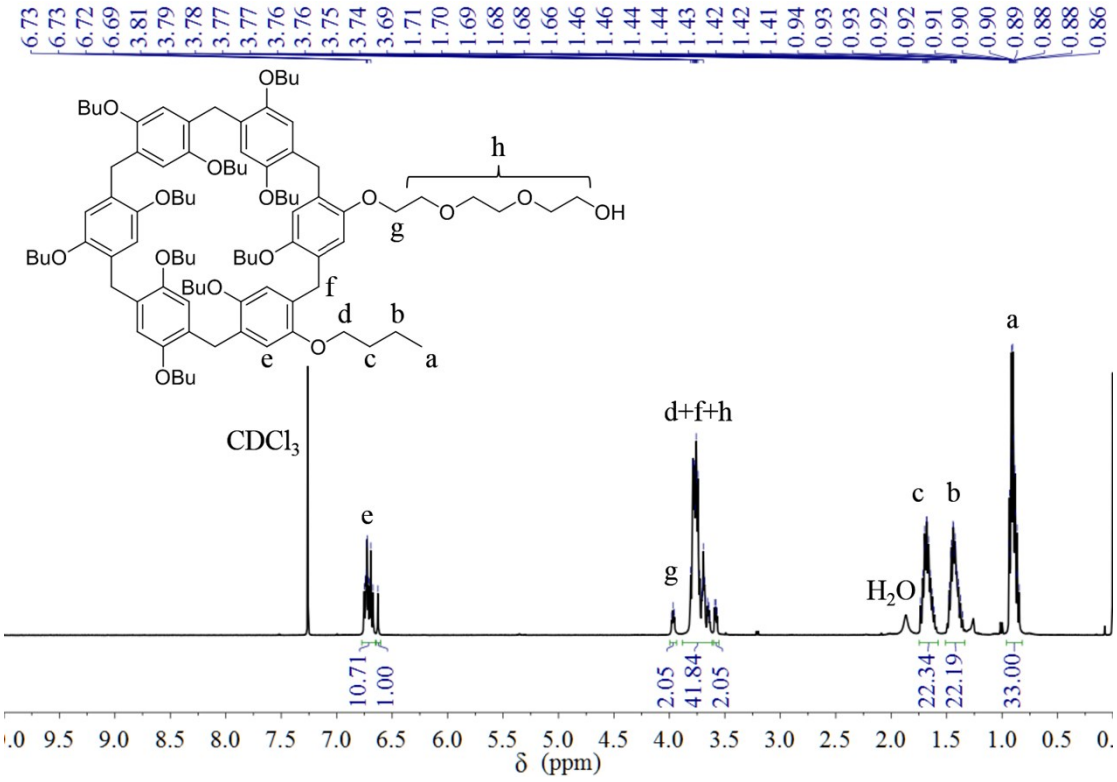


Figure S1. ^{1}H NMR spectrum of **P[6]-OH** (400 MHz, $CDCl_3$, 298 K)

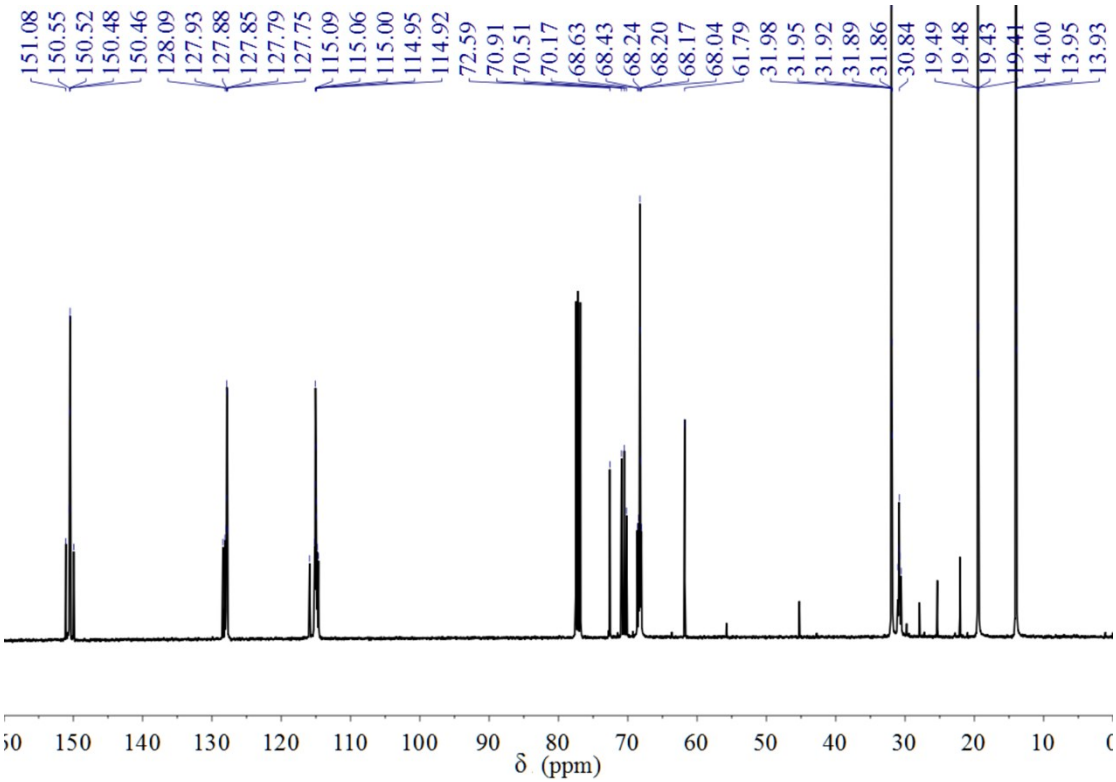


Figure S2. ^{13}C NMR spectrum of **P[6]-OH** (100 MHz, $CDCl_3$, 298 K)

1.1.2 Synthesis of butyl-pillar[6]arene functionalized chain transfer agent (P[6]-CTA)

A drop of DMF was added to a mixture of **CTA-COOH** (253.4 mg, 1 mmol) and oxalyl chloride (255.2 mg, 2 mmol) in dry dichloromethane (4 mL) under argon. After the reaction was stirred at room temperature for 1 h, the solvent, the excess of oxalyl chloride and catalytic amount of DMF were removed under vacuum. The residue was resolved in dry dichloromethane (4 mL). Then **P[6]-OH** (1.34 g, 0.9 mmol) and triethylamine (203 mg, 2 mmol) was added to the solution and the reaction was stirred overnight at room temperature. The reaction mixture was filtered and the filtrate was concentrated under vacuum. The residue was purified by flash chromatography (PE/EA = 100:1 - 40:1, v/v) to a yellow solid (1.06 g, 0.618 mmol, 61.8%). ^1H NMR (400 MHz, $CDCl_3$, 298 K) δ(ppm): 6.85 – 6.50 (m, 12H, Ar*H*), 4.31 – 4.17 (m, 2H, –CH_2OCO–), 3.98 (t, *J* = 5.0 Hz, 2H, –OCH_2–), 3.86 – 3.55 (m, 43H, Ar–CH_2–Ar & Ar–OCH_2– & –OCH_2CH_2O–), 3.17 (d, *J* = 6.8 Hz, 2H, –SCH_2CH–), 2.03 – 1.80 (m, 1H, –SCH$_2$C*H*–), 1.76 – 1.56 (m, 28H, Ar–OCH$_2$CH_2– & –(CH$_3$)$_2$C–), 1.49 – 1.31 (m,

22H, –CH_2CH$_3$), 0.98 (d, J = 6.7 Hz, 6H, –(CH$_3$)$_2$CH–), 0.95 – 0.79 (m, 33H, –CH_3). ^{13}C NMR (100 MHz, CDCl$_3$, 298 K) δ(ppm): 221.7, 173.0, 151.1, 150.6, 150.6, 150.6, 150.5, 150.5, 150.0, 128.5, 128.1, 128.0, 127.9, 127.9, 127.8, 116.0, 115.2, 115.2, 115.1, 115.1, 115.0, 115.0, 114.9, 114.6, 71.0, 70.8, 70.3, 69.0, 68.7, 68.5, 68.3, 68.3, 68.3, 68.1, 65.2, 56.1, 45.3, 32.0, 32.0, 32.0, 31.9, 31.2, 30.9, 30.8, 30.5, 28.0, 25.4, 22.2, 19.6, 19.5, 19.5, 19.5, 14.1, 14.0, 14.0. HR-ESI-MS: *m/z* Calcd for C$_{95}$H$_{138}$O$_{16}$Na [M+Na]$^+$: 1737.9978; found: 1737.9981.

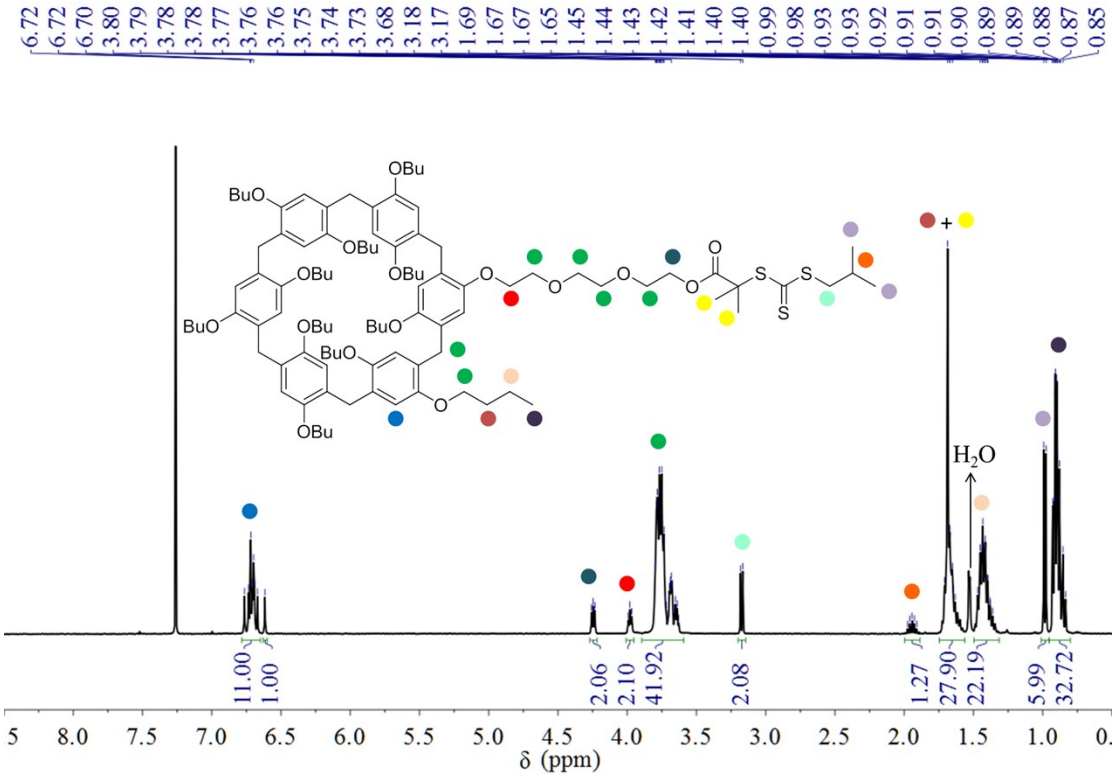


Figure S3. ^{1}H NMR spectrum of **P[6]-CTA** (400 MHz, CDCl$_3$, 298 K)

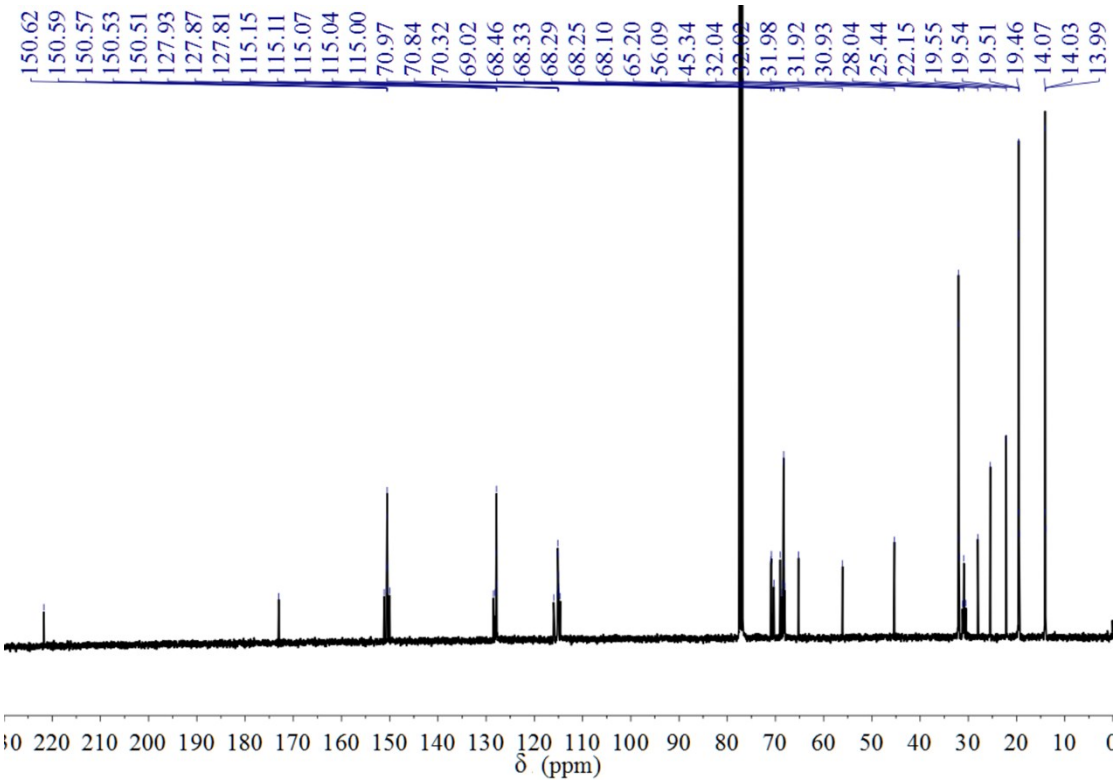


Figure S4. ^{13}C NMR spectrum of **P[6]-CTA** (100 MHz, $CDCl_3$, 298 K)

1.1.3 Synthesis of poly(*N*-isopropylacrylamide)-pillar[6]arene (PNIPAM-P[6]) via reversible addition-fragmentation chain transfer (RAFT) polymerization

P[6]-CTA (85.7 mg, 0.05 mmol), NIPAM (679.0 mg, 6 mol) and AIBN (1.64 mg, 0.01 mmol) were dissolved in DMF (3 mL) in a 10 ml round-bottom flask. After purged with argon for 20 minutes at 0 °C, the mixture was immediately transferred to a preheated 60 °C oil bath and stirred for 5 h. the resulting mixture was quenched by liquid N_2 and precipitated in diethyl ether for three times. The polymer was obtained as a light yellow power (448.0 mg, 58.6%, $M_{n,GPC}$ =14.3 kDa, PDI =1.18, $M_{n,\ NMR}$ =15.7 kDa) after drying under vacuum at room temperature for 24 h.

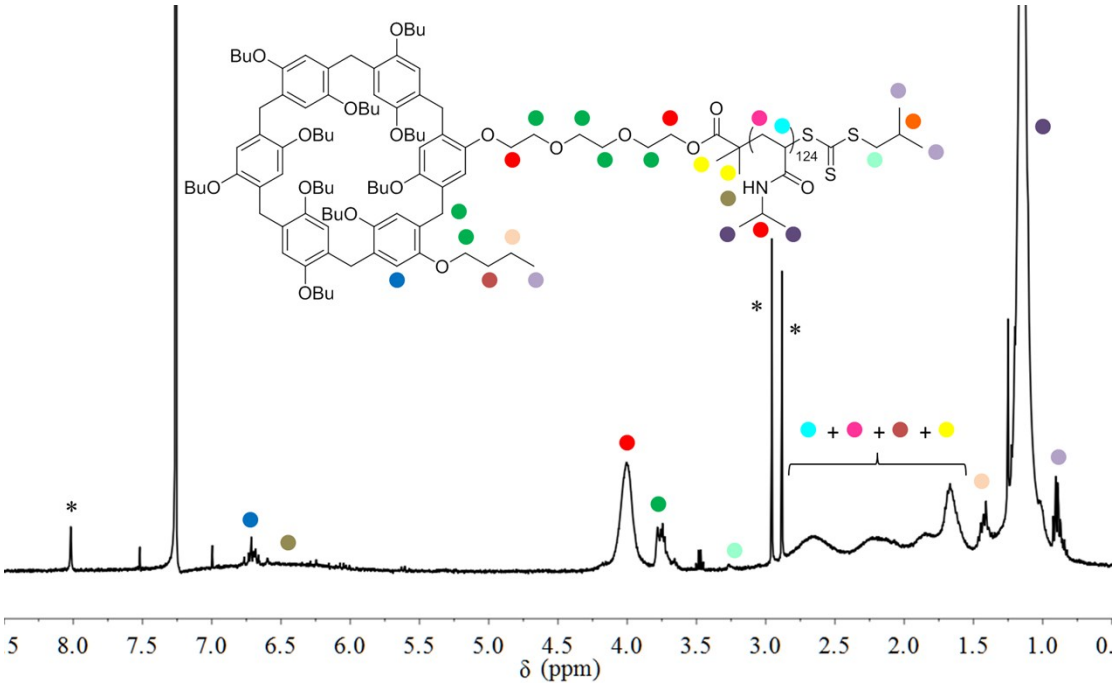


Figure S5. ^{1}H NMR spectrum of **PNIPAM-P[6]** (400 MHz, $CDCl_3$, 298 K) (* indicates the signals from DMF solvent)

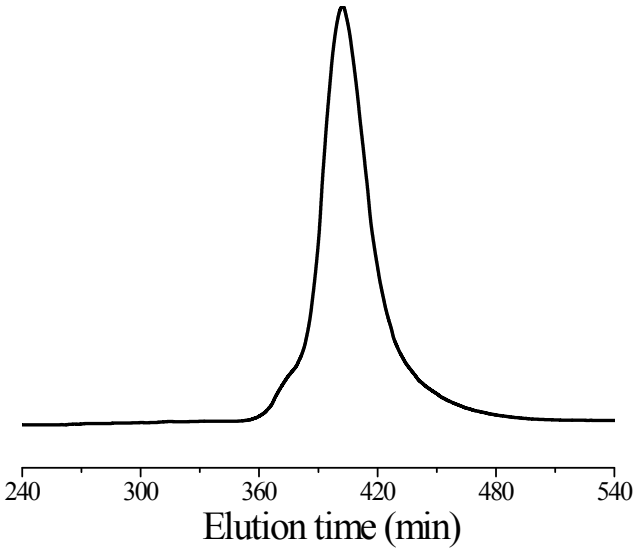
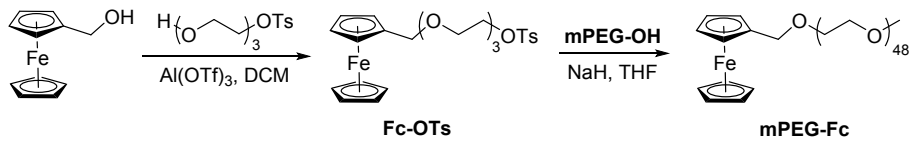


Figure S6. GPC curve of **PNIPAM-P[6]**. Eluent: DMF with 0.5 mg/mL LiBr

1.2 Synthesis of poly(ethylene glycol methyl ether)-ferrocene (mPEG-Fc)



Scheme S2. Synthetic routes of ferrocene end-functionalized polymer **mPEG-Fc**

1.2.1 Synthesis of tosylated triethylene glycol mono-ferrocene (Fc-OTs)

To a solution of hydroxymethyl ferrocene (1.00 g, 4.6 mmol) and triethylene glycol mono-tosylate (1.55 g, 5.1 mmol) in dry dichloromethane (20 mL), aluminum triflate (44 mg, 0.092 mmol) was added under argon. The mixture was stirred overnight at room temperature, and quenched with 5% aqueous Na_2CO_3 solution (20 mL). Then, the mixture was extracted with dichloromethane (3 × 20 mL). The organic phase was combined and dried over anhydrous Na_2SO_4. The crude product was further purified by silica-gel column chromatography (PE/EA = 10:1 – 4:1, v/v) to afford the target product **Fc-OTs** as an orange oil (0.93 g, 3.5 mmol, 40%). ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ(ppm): 7.78 (d, *J* = 8.0 Hz, 2H, –OTs), 7.32 (d, *J* = 7.9 Hz, 2H, –OTs), 4.29 (s, 2H, –C*H*$_2$–Fc), 4.23 (s, 2H, substituted Cp ring), 4.19 – 4.03 (m, 9H, unsubstituted Cp ring & substituted Cp ring & –C*H*$_2$OSO$_2$–), 3.65 (t, 2H, –C*H*$_2$CH$_2$OSO$_2$–), 3.54 (s, 8H, –OC*H*$_2$C*H*$_2$O–), 2.42 (s, 3H, Ar-C*H*$_3$). ^{13}C NMR (100 MHz, $CDCl_3$, 298 K) δ(ppm): 144.8, 133.0, 129.9, 128.0, 83.4, 70.8, 70.7, 70.5, 69.7, 69.5, 69.3, 68.9, 68.7, 68.7, 68.6, 21.7. HR-ESI-MS: *m/z* Calcd for $C_{95}H_{138}O_{16}Na$ $[M+Na]^+$: 525.1005; found: 525.1007.

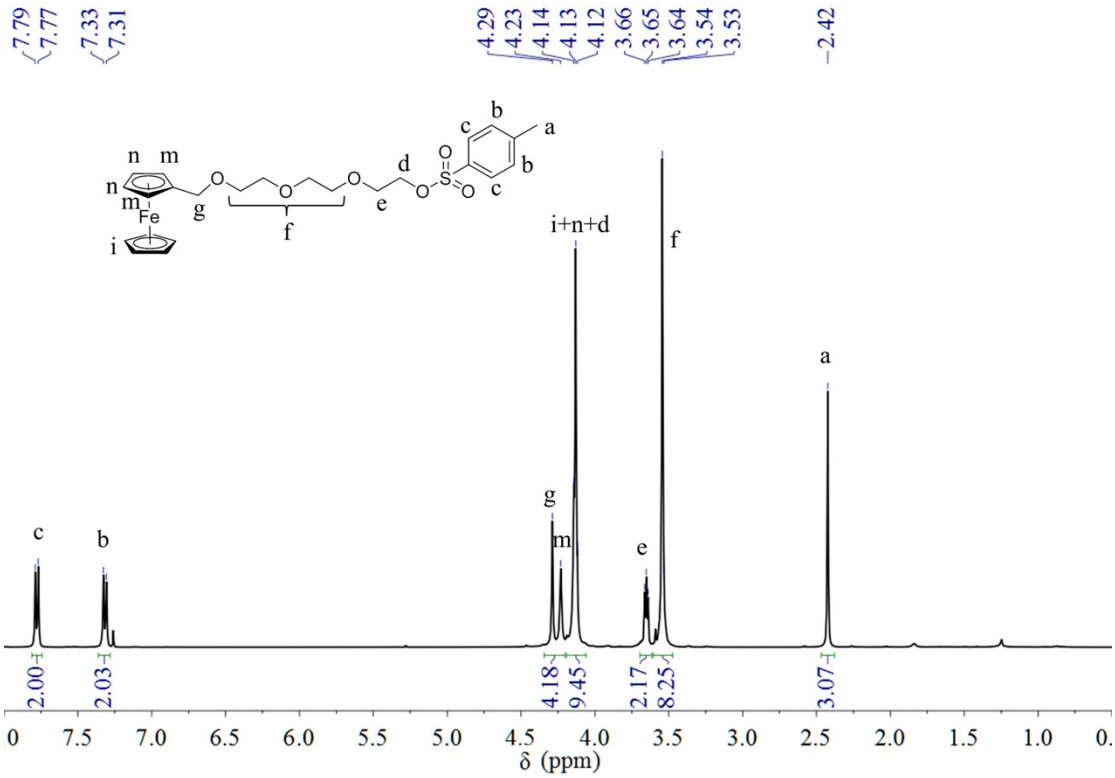


Figure S7. ^{1}H NMR spectrum of **Fc-OTs** (400 MHz, $CDCl_3$, 298 K)

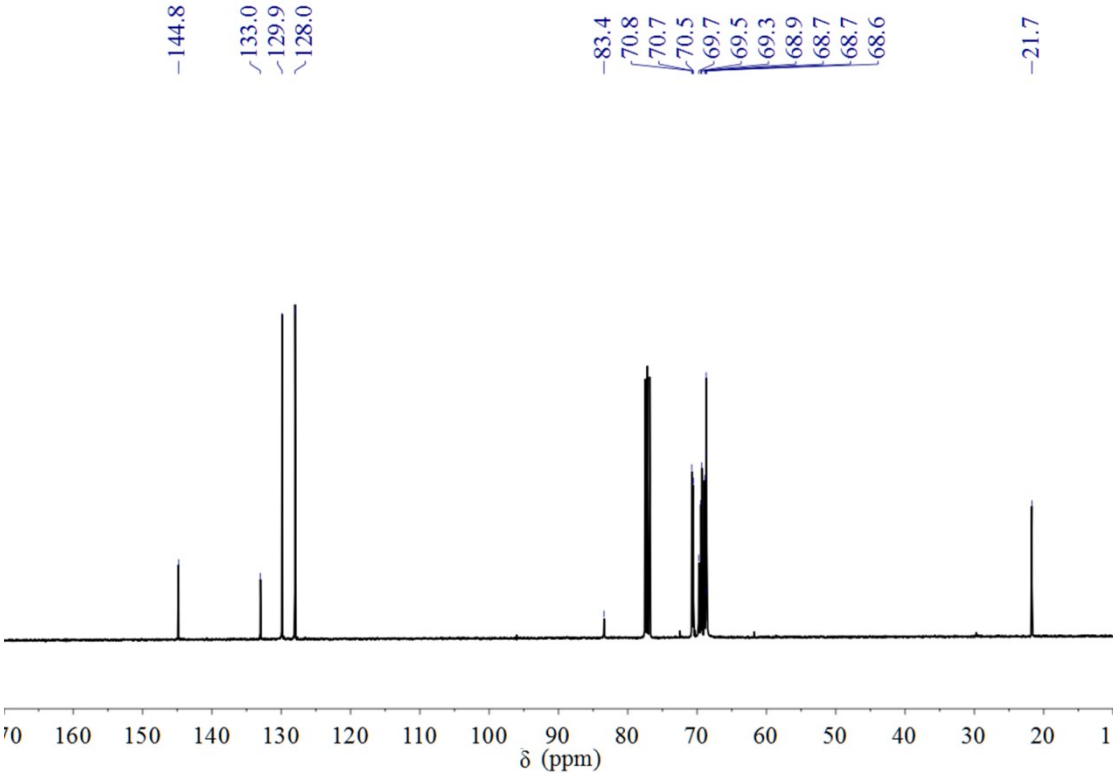


Figure S8. ^{13}C NMR spectrum of **Fc-OTs** (100 MHz, $CDCl_3$, 298 K)

1.2.2 Synthesis of ferrocene modified poly(ethylene glycol methyl ether) (mPEG-Fc)

A solution of mPEG-OH (0.6 g, 0.3 mmol) in tetrahydrofuran (5 mL) was added drop-wise to a mixture of sodium hydride (60 mg, 1.5 mmol) in tetrahydrofuran (5 mL) and the mixture was refluxed overnight. Then a solution of Fc-OTs (225.9 mg, 0.45 mmol) in tetrahydrofuran (5 mL) was added to the mixture. After stirring for 48 h, the reaction mixture was filtered and the filtrate was precipitated in diethyl ether for three times. The polymer mPEG-Fc obtained as a yellow solid (0.59 g, 84.3%) after drying under vacuum at room temperature for 24 h.

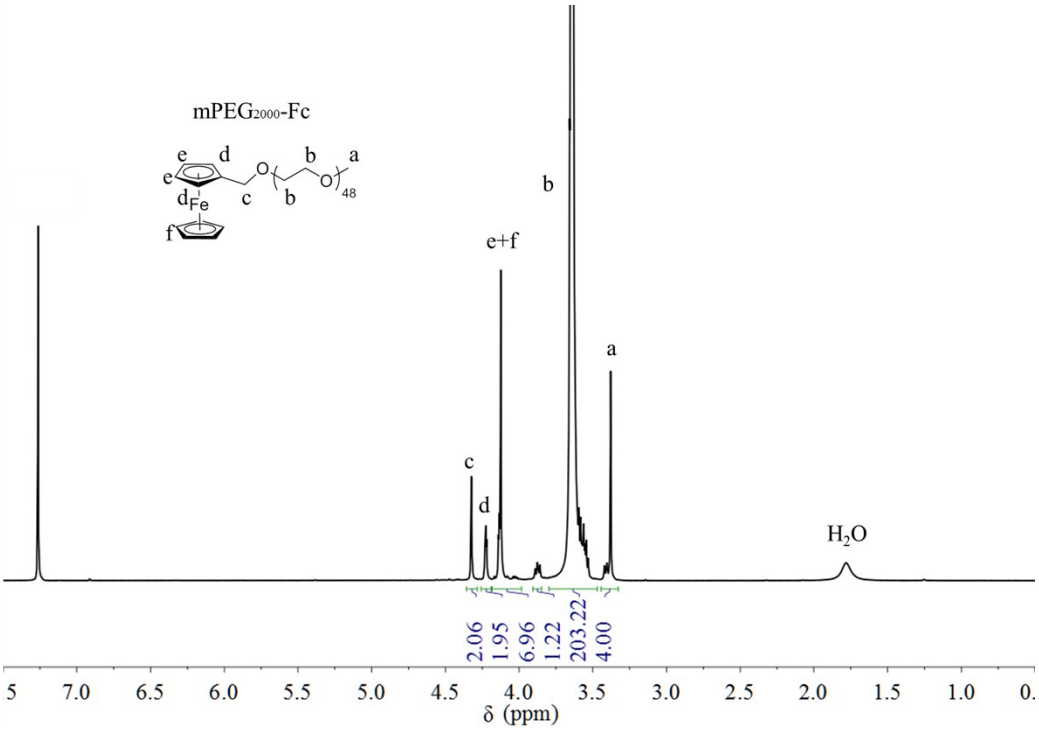


Figure S9. ^{1}H NMR spectrum of **mPEG-Fc** (400 MHz, $CDCl_3$, 298 K)

2. Host-Guest Complexation Study between Host Polymer and Guest Polymer by ^{1}H NMR Spectroscopy

The binding properties of water soluble pillar[6]arene and ferrocene derivative in water driven by the hydrophobic effect was investigated in our previous work,[S1] and the association constant of them in water ($(1.27 \pm 0.42) \times 10^5$ M^{-1}) is much stronger than that of hydrophobic pillar[6]arene and ferrocene in organic solvents (18 ± 0.5 M^{-}

[1]). In the present work, it is a little bit different from the previous cases, because the pillar[6]arene moiety in **PNIPAM-P[6]** is hydrophobic but **PNIPAM** chain in **PNIPAM-P[6]** is hydrophilic at 25 °C. Therefore, the host-guest interaction would be investigated between hydrophobic pillar[6]arence moiety and hydrophobic ferrocene moiety or hydrophilic ferrocenium (oxidation state) in water at 25 °C or 37 °C.

2.1 The ^{1}H NMR study of the complexation of PNIPAM-P[6] with mPEG-Fc in water at 25 °C

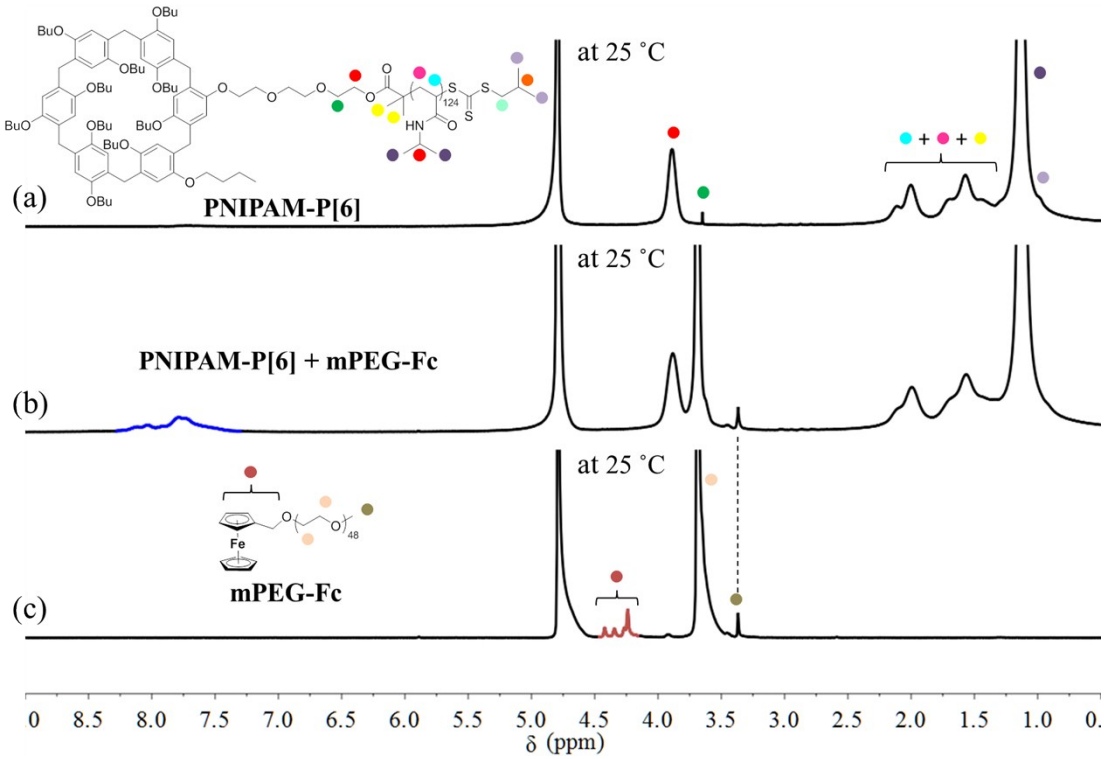


Figure S10. ^{1}H NMR spectra (D_2O, 400 MHz, 25 ˚C) of (a) 1 mM **PNIPAM-P[6]**, (b) 1 mM **PNIPAM-P[6]** and 1 mM **mPEG-Fc**, (c) 1 mM **mPEG-Fc.**

The typical ^{1}H NMR signal of the phenyl protons of terminal **P[6]** of **PNIPAM-P[6]** was not observed at 25 °C in D_2O (Figure S10a) due to the formation of micelles from **PNIPAM-P[6]** with hydrophobic **P[6]** moiety trapped inside. However, after the addition of 1.0 equiv. of **mPEG-Fc** at 25 °C followed by sonication, a set of significant proton signals of the phenyl protons of **P[6]** were observed in the downfield region; In the meanwhile, the proton signals of Fc moiety of **mPEG-Fc** disappeared in the original position**,** which could move towards upfield and were

overlapped by other proton signals (Figure S10b and S10c). This results suggested the formation of the polymeric inclusion complex between **PNIPAM-P[6]** and **mPEG-Fc** through the host-guest interaction at 25 °C in water.

2.2 The ^{1}H NMR study of the complexation of cobaltocenium with PNIPAM-P[6] in water at 37 °C and 25 °C, respectively

Diamagnetic cobaltocenium (Cob^+) that is an analogue of paramagnetic ferrocenium was applied for the study of its complexation with host polymer **PNIPAM-P[6]** at 37 ˚C and 25 ˚C, respectively, by ^{1}H NMR.

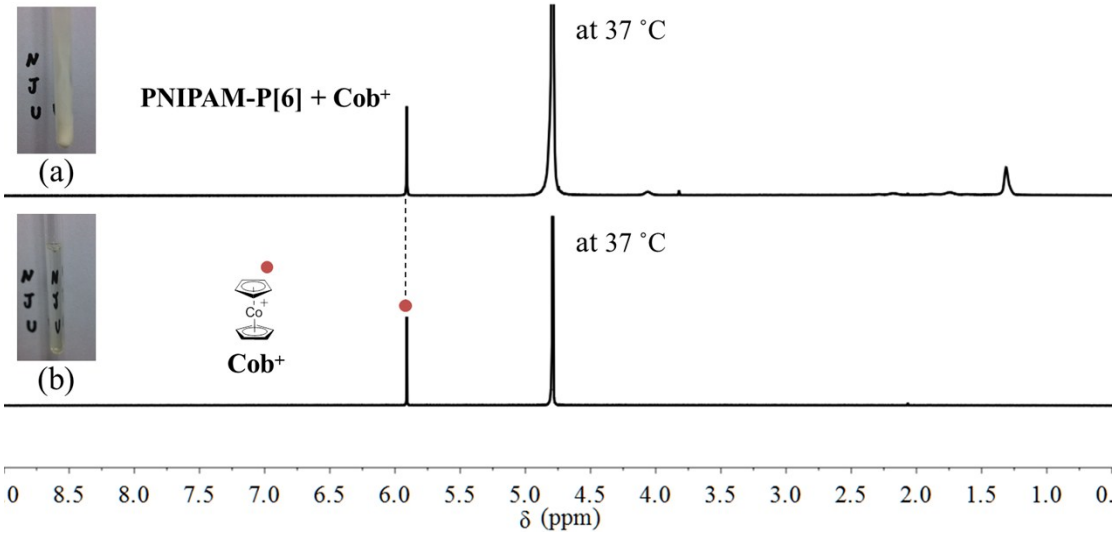


Figure S11. ^{1}H NMR spectra (D_2O, 600 MHz, 37 ˚C) of (a) 1 mM **PNIPAM-P[6]** and 1 mM **Cob$^+$ PF$_6^-$**, (b) 1 mM **Cob$^+$ PF$_6^-$**.

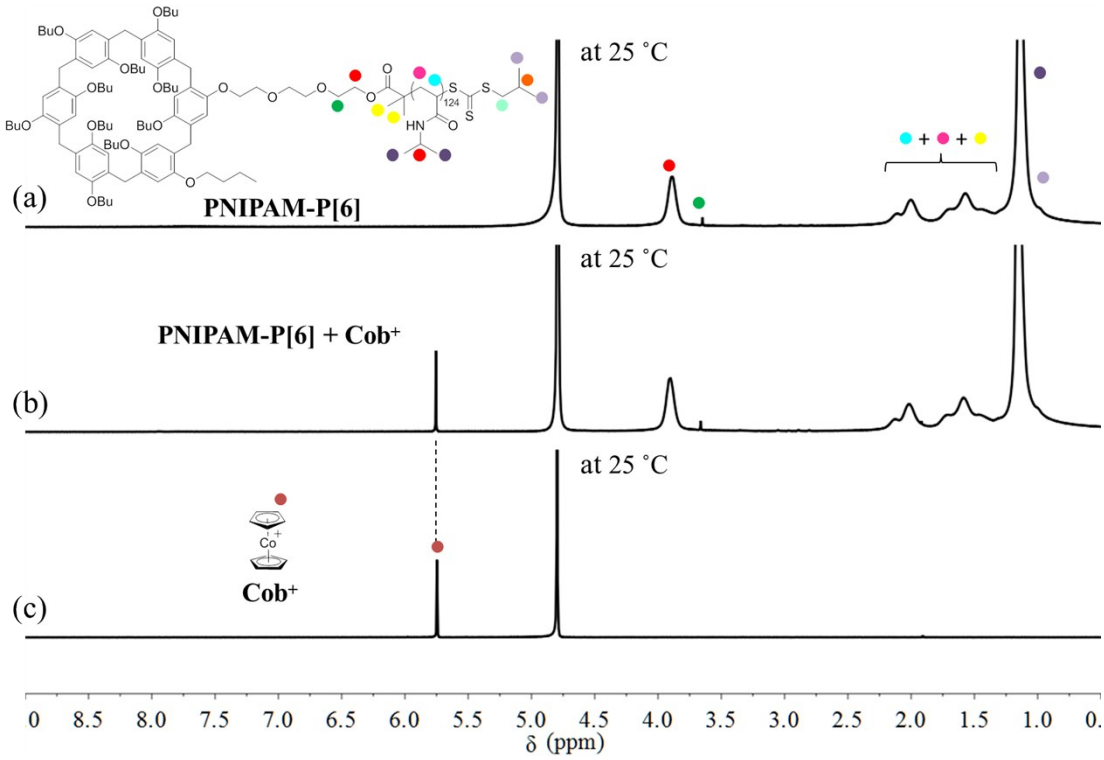


Figure S12. ^{1}H NMR spectra (D_2O, 400 MHz, 25 ˚C) of (a) 1 mM **PNIPAM-P[6]**, (b) 1 mM **PNIPAM-P[6]** and 1 mM **Cob$^+$PF$_6^-$**, (c) 1 mM **Cob$^+$ PF$_6^-$**.

All above results indicated that no host-guest interaction between Cob$^+$ and **PNIPAM-P[6]** in water was observed either at 37 ˚C or 25 ˚C, which could be applied for **Fc$^+$** case. Therefore, it is supported that the host-guest interactions that were based on the hydrophobic effect between **P[6]**-based polymeric host and Fc-based polymeric guest at 37 ˚C were destroyed upon addition of $AgNO_3$, because Fc moiety of guest polymer **mPEG-Fc** was oxidized into ferrocenium unit by $AgNO_3$, which became hydrophilic unit and was solvated by water, leading to the immediate aggregation of hydrophobic host polymer **PNIPAM-P[6]** at 37 ˚C in water and disassembly of vesicles.

3. Critical aggregation concentration (CAC)

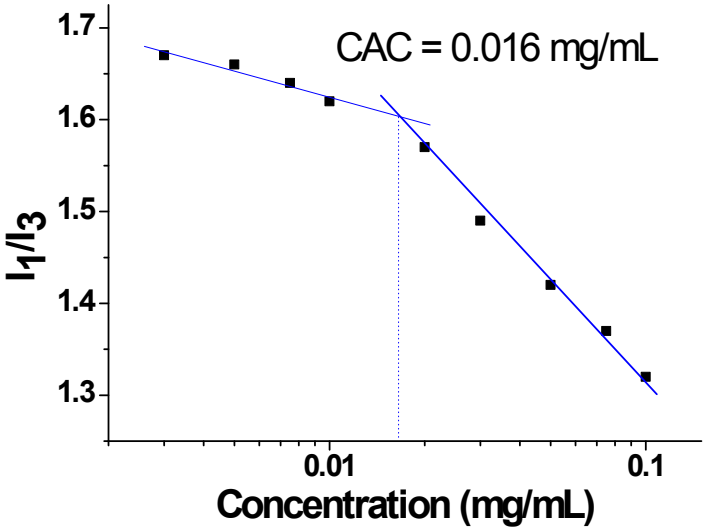


Figure S13. Determination of CAC for the supramolecular vesicles of **PNIPAM-P[6]⊃mPEG-Fc** using the fluorescent method with pyrene as a probe at 37 °C.

4. Phenomenon of vesicles after adding oxidizing agents at 37 °C

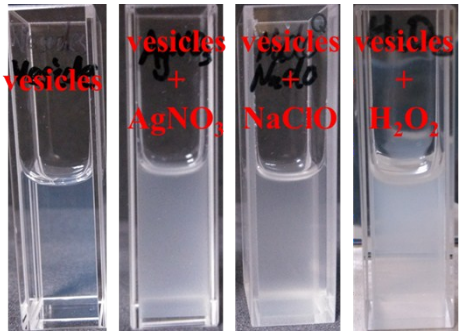


Figure S14. Comparison of states among vesicular solution of **PNIPAM-P[6]⊃mPEG-Fc**, vesicular solution added with $AgNO_3$ (4 mM), vesicular solution added with NaClO (4 mM), and vesicular solution added with H_2O_2 (4 mM) at 37 °C.

5. References

S1. Duan, Q.; Cao, Y.; Li, Y.; Hu, X.; Xiao, T.; Lin, C.; Pan, Y.; Wang, L. *J. Am. Chem. Soc.* **2013**, *135*, 10542-10549.

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S3. Xia, W.; Hu, X.-Y.; Chen, Y.; Lin, C.; Wang, L. *Chem. Commun.* **2013**, *49*, 5085-5087.

S4. Xia, W.; Ni, M.; Yao, C.; Wang, X.; Chen, D.; Lin, C.; Hu, X.-Y.; Wang, L. *Macromolecules* **2015**, *48*, 4403-4409.